STRUCTURE ANALYSIS IN HERBICIDE DESIGN

H. G. McFadden and J. L. Huppatz
Division of Plant Industry, CSIRO, GPO Box 1600, Canberra 2601.

Summary. Common features of molecules known to inhibit herbicide target sites may provide a basis for the design of new herbicidal molecules. The use of simple computer graphics allows visualisation of the structures of compounds. Molecules interacting with a common binding site can be compared and features of the shape and surface properties likely to influence binding to the receptor can be identified. Some inhibitors of the enzyme acetyl coenzyme-A carboxylase and of photosynthetic electron transport are examined for common structural characteristics which may reflect on the topography of the respective binding sites. Such information can be used to generate new ideas for the design of novel active molecules.

INTRODUCTION

The strategies used to develop useful herbicides are rapidly evolving to meet increasing pressure for highly potent, plant specific biocides with minimal environmental persistence. In order to achieve this, potential herbicides should be designed to block a specific, critical plant metabolic process. It is only relatively recently, though, that detailed knowledge of herbicide sites of action has become available. It is remarkable that established herbicides interact with only a few sites, despite the myriad possibilities in plant biochemical pathways. Furthermore, with few exceptions, the target sites now recognised act as receptors for herbicides of more than one chemical class.

There is a possibility that the number of available target sites for herbicides, and pesticides generally, may be relatively small (1). This raises the question as to whether these sites have common properties rendering them particularly susceptible to the effects of xenobiotics. Herbicide targets susceptible to several diverse chemical classes are attractive areas for study, both in terms of the nature and topography of the sites themselves and in terms of the relationships between the structure and properties of the inhibitor molecules.

STRUCTURE ANALYSIS

Before the advent of computers, chemists used physical models of balls and wire to visualize the structures of compounds they synthesized. It is now possible to build pictures of compound structures with inexpensive programs that run on personal computers. Some idea of the most likely conformation of a molecule, based on minimum energy calculations, may also be obtained. These structures can be rotated, manipulated and superimposed to give a qualitative representation of the structural similarities between different compounds and hence a picture of the requirements of the binding domain on the receptor. More sophisticated, hardware-intensive (and therefore expensive) programs are required to obtain quantitative results regarding common volumes occupied by ligands and to analyse electronic and other effects in detail, but interesting information can be still be obtained with the simpler programs. In the study of herbicides, simple computer graphics can be used to compare structural relationships and spatial orientations of different classes of inhibitor binding to the same receptor, as shown by considering diverse chemical groups inhibiting two established herbicide target sites, one in lipid biosynthesis, the other in photosynthesis.

LIPID BIOSYNTHESIS

Two major classes of grass herbicide, the aryloxyphenoxypropionates (haloxyfop, fluazifop, diclofop-methyl) and the cyclohexanediones (tralkoxydim, sethoxydim, cycloxydim) inhibit acetyl coenzyme-A carboxylase (ACC), a critical enzyme in lipid biosynthesis (2).

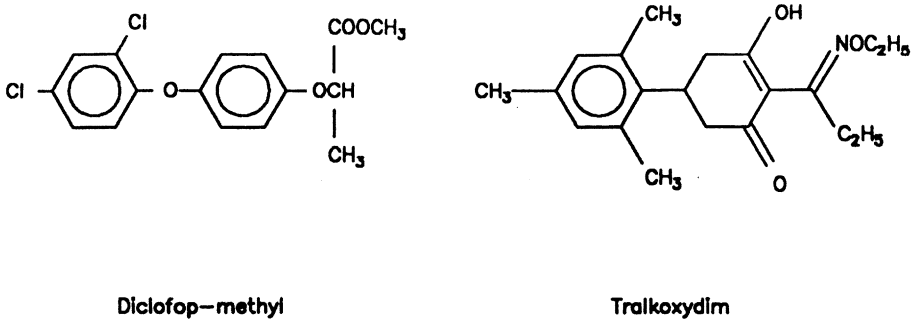

Figure 1. Chemical structures of diclofop-methyl and tralkoxydim

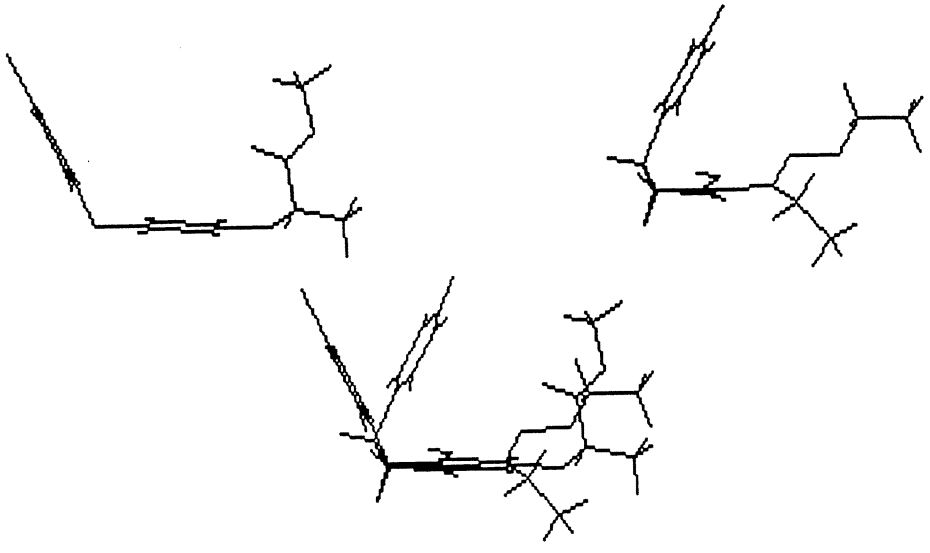

Figure 2. Structures of diclofop-methyl (left), tralkoxydim (right), and both structures superimposed (below).

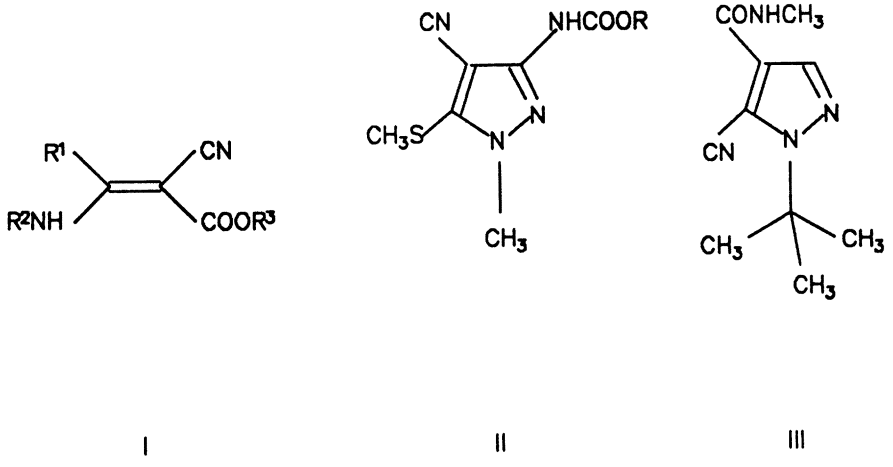

Figure 3. Chemical structure of three PSII inhibitors.

Binding studies with examples of these two classes of compounds have shown competitive binding, which tends to support the hypothesis that the compounds are binding to the same portion of the enzyme surface (3). A detailed study of the structural properties of a cyclohexanedione series has defined some of the parameters giving efficient binding in this series (4).

Superimposition of diagrams of the structures of the diclofop and tralkoxydim shows that there are significant similarities in the overall shapes of the two molecules. Thus, it appears that these molecules, despite marked differences in their chemical properties, share similar external surface characteristics. It is therefore conceivable that they occupy the same niche on the enzyme. This adds further support to the idea that both classes of compounds are interacting with the same portion of the protein. It might therefore be possible to combine the structural data from the two series to maximize the information available regarding the binding requirements of this site.

PHOTOSYSTEM II INHIBITORS

The herbicide binding site in the photosystem II (PSII) complex in chloroplasts is one of the most intensively studied herbicide receptors. The diversity in the chemical nature of inhibitors is great and includes the urea (diuron, monuron), triazine (atrazine, simazine), triazinone (metribuzin), uracil (bromacil) and phenol (dinoseb, ioxynil) herbicides. These compounds all bind to a 32kD polypeptide, the D_1 or Q_B protein, in the PSII complex. The dilemma for the herbicide chemist is how to rationalise the different chemical types in terms of a common binding site. A great step forward in the information available about this site was made when the structure of the corresponding bacterial reaction centre was deduced from x-ray crystallography (5). Unfortunately, many plant herbicides are inactive in the bacterial system, limiting the extrapolations that can be made from the bacterial to the plant system.

The cyanoacrylate family of PSII inhibitors (I) are characterised by high potency and flexibility in chemical structure in which activity is extremely sensitive to minor structural variation. Recently, other classes of PSII inhibitors have been described (6,7) based on the pyrazole ring system (II, III). These heterocylic compounds contain structural features common to cyanoacrylate molecules. Superimposition of structures of an active cyanoacrylate and the two pyrazole derivatives shows that there are portions of overlap and regions which might occupy a common binding domain. The degree of overlap depends somewhat on the relative orientations of the compounds, which is at the whim of the investigator in the current absence of any evidence regarding the orientation of these compounds on the site.

However, an interesting question is raised by considering these two types of compound. If the overlap of the cyanoacrylate and pyrazoles is valid, is it possible to use the extensive database that has been accumulated relating the structure and activity of cyanoacrylates to design a novel, active pyrazole?

CONCLUSIONS

At this stage the study of known herbicide target sites and their inhibitors raises more questions than answers, but it is hoped that the pursuit of these answers will yield, not only novel commercial herbicidal activity, but also information which will provide support to the notion that rational herbicide design is a realisable goal.

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